6. Glycemic Goals, Hypoglycemia, and Hyperglycemic Crises: Standards of Care in Diabetes—2026

*American Diabetes Association Professional Practice Committee for Diabetes**

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ASSESSMENT OF GLYCEMIC STATUS

Glycemic status is assessed by A1C measurement, blood glucose monitoring (BGM) by capillary (finger-stick) devices, and different continuous glucose monitoring (CGM) metrics such as time in range (TIR), time below range (TBR), time above range (TAR), glucose management indicator (GMI), coefficient of variation, and mean glucose. Clinical trials of interventions that lower A1C have demonstrated the benefits of improved glycemia with respect to long-term diabetes complications. Glucose monitoring via CGM or BGM (discussed in detail in section 7, "Diabetes Technology") is useful for diabetes self-management, can provide nuanced information on glucose responses to meals, physical activity, and medication changes, and is particularly useful for optimal medication management and safety in individuals taking insulin. CGM serves an increasingly important role in optimizing the effectiveness and safety of treatment in many people with type 1 diabetes, type 2 diabetes, diabetes in pregnancy, and other forms of diabetes (e.g., cystic fibrosis–related diabetes). Individuals on a variety of insulin treatment plans benefit from CGM with improved glucose levels, decreased hypoglycemia, and enhanced self-efficacy (section 7, "Diabetes Technology") (1).

Glycemic Assessment

Recommendations

6.1 Assess glycemic status by A1C **A** and/or continuous glucose monitoring (CGM) metrics such as time in range, time above range, and time below range. **B** Fructosamine or CGM can be used for glycemic monitoring when an alternative to A1C is required. **B**

6.2 Assess glycemic status at least two times a year, and more frequently (e.g., every 3 months) for individuals not meeting glycemic goals or with recent treatment changes, frequent or severe hypoglycemia or hyperglycemia, or changes in health status, or during periods of rapid growth and development in children and adolescents. **E**

**A complete list of members of the American Diabetes Association Professional Practice Committee for Diabetes can be found at https://doi.org/10.2337/dc26-SINT.*

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Glycemic Assessment by A1C

The A1C test is the primary tool for assessing glycemic status in both clinical practice and clinical trials, and it is strongly linked to diabetes complications (2–4). A1C reflects average glycemia over approximately 2–3 months. The performance of laboratory tests for A1C is generally excellent for National Glycohemoglobin Standardization Program (NGSP)-certified assays (ngsp.org). Thus, A1C testing should be performed routinely in all people with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether glycemic goals have been reached and maintained. Adults with type 1 or type 2 diabetes who have achieved and are maintaining glucose levels within their goal range may only need A1C testing twice a year. Individuals with less stable glucose levels, those with intensive care plans, or those not meeting their treatment goals may require more frequent testing, typically every 3 months, with additional assessments as needed. Point-of-care A1C testing can offer timely opportunities for treatment adjustments during appointments with health care professionals, although point-of-care tests may be less accurate than laboratory A1C assays (5).

The A1C test is an indirect measure of average glycemia. Factors that affect hemoglobin or red blood cells may affect A1C; see section 2, "Diagnosis and Classification of Diabetes," for details. For example, conditions that affect red blood cell turnover (e.g., hemolytic anemia and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, kidney failure, and pregnancy) can interfere with the accuracy of A1C (6). Some hemoglobin variants can interfere with some A1C assays; however, most assays in use in the U.S. are accurate in individuals who are heterozygous for the most common variants (7). A1C cannot be measured in individuals with sickle cell disease (HbSS) or other homozygous hemoglobin variants (e.g., HbEE), since these individuals lack HbA (8). In individuals with conditions that interfere with the interpretation of A1C, alternative approaches to monitoring glycemic status should be used, including self-monitoring of blood glucose, CGM, and/or the use of glycated serum protein assays (discussed below). A1C does not provide a measure of glycemic variability, real-time glucose levels, or hypoglycemia. For individuals prone to glycemic variability, especially people with type 1 diabetes or type 2 diabetes with insulin deficiency and/or treatment with intensive insulin therapy, glycemic status is best evaluated by the combination of results from BGM or CGM and A1C. Discordant results between A1C and BGM or CGM can occur due to high glycemic variability, inaccurate BGM or CGM measurement, or inaccurate A1C due to the factors discussed above.

As discussed in section 2, "Diagnosis and Classification of Diabetes," there is controversy regarding the clinical significance of differences in A1C by self-reported race and ethnicity (9–12). There is an emerging understanding of genetic determinants that may modify the association between A1C and glucose levels (13). However, race and ethnicity are not good proxies for these genetic differences that are likely present in a small fraction of individuals of all racial groups. Therefore, race and ethnicity should not be considerations for how A1C is used clinically for glycemic monitoring. Limitations of laboratory tests and within-person variability in glucose and A1C underscore the importance of using multiple approaches to glycemic monitoring and further evaluation of discordant results in all racial or ethnic groups.

Serum Glycated Protein Assays as Alternatives to A1C

Fructosamine and glycated albumin are alternative measures of glycemia that are approved for clinical use for monitoring glycemic status in people with diabetes. Fructosamine reflects total glycated serum proteins (mostly albumin). Glycated albumin assays reflect the proportion of total albumin that is glycated. Due to the turnover rate of serum protein, fructosamine and glycated albumin reflect glycemia over the past 2–4 weeks, a shorter-term time frame than that of A1C. Fructosamine and glycated albumin are highly correlated in people with diabetes, and the performance of modern assays is typically excellent. Fructosamine and glycated albumin have been linked to long-term complications in epidemiologic cohort studies (14–18). However, there have been few clinical trials, and the evidence base supporting the use of these biomarkers to monitor glycemic status is much weaker than that for A1C. In people with diabetes who have conditions where the interpretation of A1C may be problematic or when A1C cannot be measured (e.g., homozygous hemoglobin variants), fructosamine or glycated albumin may be useful alternatives to monitor glycemic status (8).

Correlation Between A1C and Blood Glucose Monitoring and Continuous Glucose Monitoring

Table 6.1 provides rough equivalents of A1C and mean glucose levels based on data from the international A1C-Derived Average Glucose (ADAG) study. The ADAG study assessed the correlation between A1C and frequent BGM and CGM in 507 adults (83% non-Hispanic White) with type 1, type 2, and no diabetes (19,20). The American Diabetes Association (ADA) and the American Association for Clinical

Table 6.1—Equivalent A1C levels and estimated average glucose (eAG)

A1C (%)	A1C (mmol/mol)	eAG mg/dL*	eAG mmol/L*
5	31	97 (76–120)	5.4 (4.2–6.7)
6	42	126 (100–152)	7.0 (5.5–8.5)
7	53	154 (123–185)	8.6 (6.8–10.3)
8	64	183 (147–217)	10.2 (8.1–12.1)
9	75	212 (170–249)	11.8 (9.4–13.9)
10	86	240 (193–282)	13.4 (10.7–15.7)
11	97	269 (217–314)	14.9 (12.0–17.5)
12	108	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (19,20). Adapted from Nathan et al. (19).

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Chemistry have determined that the correlation (r = 0.92) in the ADAG trial is strong enough to justify reporting both the A1C result and the estimated average glucose (eAG) result when a clinician orders the A1C test. Clinicians should note that the mean plasma glucose numbers in **Table 6.1** are based on ∼2,700 readings per A1C measurement in the ADAG trial.

Caveats in interpretation of **Table 6.1** include that these data are from a single study published in 2008. Mean glucose in the ADAG study was calculated from a combination of measurements from an early CGM system and capillary glucose, intermittently, during a 3-month period. This older system required calibration several times a day using a self-monitoring glucose meter. It is unclear how generalizable these estimates are to mean glucose measurements obtained using modern and generally more accurate CGM systems. The comparability of A1C and mean glucose from CGM systems will depend on the number of days of CGM wear, timing of the A1C measurement relative to the CGM wear period, calibration and accuracy of both the glucose meter and the CGM system, the lag time between interstitial glucose and venous glucose (which varies among individuals and within individuals based on physical activity and health status), and any factors that affect A1C or red blood cell turnover (see section 2, "Diagnosis and Classification of Diabetes").

Glycemic Assessment by Blood Glucose Monitoring

For many people with diabetes, glucose monitoring, either using BGM by capillary (finger-stick) devices and/or CGM in addition to regular A1C testing, is key for achieving glycemic goals. Major clinical trials of insulin-treated individuals have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic management on diabetes complications (21). BGM is thus an integral component of effective therapy for individuals taking insulin. In recent years, CGM has become a standard method for glucose monitoring for most people with type 1 diabetes and people with type 2 diabetes treated with insulin. Both approaches to glucose monitoring allow people with diabetes to evaluate individual responses to therapy and assess whether glycemic goals are being safely achieved. The specific needs and goals of individuals with diabetes should dictate BGM frequency and timing. Please refer to section 7, "Diabetes Technology," for a more complete discussion of the use of BGM and CGM.

Glycemic Assessment by Continuous Glucose Monitoring

CGM is particularly useful in people with diabetes who are at risk for hypoglycemia and in people with type 1 diabetes (21). Use of CGM in type 2 diabetes (as well as in several other forms of diabetes) is growing, especially in people who are taking insulin. TIR is a useful metric of glycemic status. A 10- to 14-day CGM assessment of TIR, with CGM wear of 70% or higher, and other CGM metrics can be used to assess glycemic status and are useful in clinical management (22–26). TIR, and especially mean CGM glucose, correlates with A1C (27–31). TBR (<70 and <54 mg/dL [<3.9 and <3.0 mmol/L]) and TAR (>180 mg/dL [>10.0 mmol/L]) are useful parameters for insulin dose adjustments, reevaluation of the treatment plan, and real-time detection, prevention, and treatment of hypoglycemia and significant hyperglycemia. High coefficient of variation (>36%) has also been related to occurrence of hypoglycemia (32). The international consensus on CGM provides guidance on CGM metrics (**Table 6.2**) and their clinical interpretation (33). To make these metrics actionable, standardized reports with visual summaries have been implemented (33) and help individuals with diabetes and health care professionals interpret the data to guide treatment decisions (27,30). Glucose data can be analyzed remotely to guide adjustment to diabetes therapy (34–36).

Published data from two retrospective studies suggest a strong correlation between TIR and A1C, with a goal of >70% TIR aligning with an A1C of ∼7% (∼53 mmol/mol) (25,28). Note that the goals of therapy displayed in **Table 6.2**

Table 6.2—CGM metrics for clinical care in nonpregnant individuals with type 1 or type 2 diabetes

Metric	Interpretation	Goals
Metrics for valid CGM wear		
Wear time	Number of days CGM device is worn	≥14-day wear for pattern management
Active percentage time	Percent of time CGM device is active	70% of time active out of 14 days
Glycemic metrics		
Mean glucose	Mean of glucose values	*
Glucose management indicator (GMI)	Calculated value approximating A1C (not always equivalent)	*
Glucose coefficient of variation (CV)	Spread of glucose values	≤36%†
TAR >250 mg/dL (>13.9 mmol/L)	Percent of time in level 2 hyperglycemia	<5% (most adults); <10% (older adults with complex/intermediate health)
TAR >180 mg/dL (>10 mmol/L)	Percent of time in level 1 hyperglycemia	<25% (most adults); <50% (older adults with complex/intermediate health)‡
TIR 70–180 mg/dL (3.9–10.0 mmol/L)	Percent of time in range	>70% (most adults); >50% (older adults with complex/intermediate health)
TBR <70 mg/dL (<3.9 mmol/L)	Percent of time in level 1 hypoglycemia	<4% (most adults); <1% (older adults with complex/intermediate health)§
TBR <54 mg/dL (<3.0 mmol/L)	Percent of time in level 2 hypoglycemia	<1%

CGM, continuous glucose monitoring; TAR, time above range; TBR, time below range; TIR, time in range. *Goals for these values are not standardized. †Some studies suggest that lower coefficient of variation targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. ‡Goals are for level 1 and level 2 hyperglycemia combined. §Goals are for level 1 and level 2 hypoglycemia combined. Adapted from Battelino et al. (33).

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serve as values to guide changes in therapy. For older adults with complex or intermediate health using CGM, the recommended percent time spent in goal range of 70–180 mg/dL is 50% (or 12 h per day) and the recommended time spent in hypoglycemia of less than 70 mg/dL should not be more than 1%, or 15 min per day, to minimize hypoglycemia risk (33,37–40). In this population, more permissive hyperglycemia is allowed (up to 50% of the time in 24 h) if required to prevent hypoglycemia.

GLYCEMIC GOALS

Recommendations

6.3a An A1C goal of <7% (<53 mmol/mol) is appropriate for many nonpregnant adults without severe hypoglycemia or hypoglycemia affecting health or quality of life. **A**

6.3b A goal time in range of >70% in people using CGM is appropriate for many nonpregnant adults. **B**

6.3c A goal percent time <70 mg/dL (<3.9 mmol/L) of <4% (or <1% for older adults) and a goal percent time <54 mg/dL (<3.0 mmol/L) of <1% are recommended in people using CGM to prevent hypoglycemia. Deintensify or modify therapy if these goals are not met. **B**

6.4 Lower A1C goals (e.g., <6.5% [<48 mmol/mol]) may be appropriate for individuals with diabetes with good health and function and low treatment risks (e.g., hypoglycemia) and burdens (see **Fig. 6.1**). **B**

6.5 Less stringent glycemic goals may be appropriate for individuals with significant cognitive and/or functional limitations, frailty, or severe comorbidities or where the harms of treatment, including hypoglycemia, are greater than the benefits. **B**

6.6 Deintensify hypoglycemia-causing medications (insulin, sulfonylureas, or meglitinides), or switch to a medication class with lower hypoglycemia risk, for individuals who are at high risk for hypoglycemia, within individualized glycemic goals. **B**

6.7 Deintensify diabetes medications for individuals for whom the harms and/or burdens of treatment may be greater than the benefits, within individualized glycemic goals. **B**

6.8 Reassess glycemic goals based on the individualized criteria shown in **Fig. 6.1**. **E**

6.9 Set a glycemic goal during consultations to improve outcomes. **A**

For all populations, it is critical that glycemic goals be woven into an individualized, person-centered strategy (41). The glycemic goals for many nonpregnant adults are shown in **Table 6.3**, and **Fig. 6.1** summarizes how A1C and CGM goals should be individualized by each person's health, function, capacity for self-management, potential for the treatment plan to cause hypoglycemia, and other modifying factors. For example, less stringent goals are appropriate for individuals with significant functional and cognitive impairments. For more details regarding glycemic goals in older adults, please refer to section 13, "Older Adults." For glycemic goals in children and adolescents, please refer to section 14, "Children and Adolescents." For glycemic goals during pregnancy, please refer to section 15, "Management of Diabetes in Pregnancy."

Health care professionals should engage in shared decision-making with the individual (as well as with family members and care partners) to establish treatment goals and should adjust goals to improve safety and medication-taking behavior particularly in the setting of changing health status. Setting specific glycemic (and other) treatment goals during clinical consultations has been demonstrated to improve glycemic outcomes for individuals with diabetes (42).

Glucose Lowering and Microvascular Complications

The Diabetes Control and Complications Trial (DCCT) (43), a prospective randomized controlled trial of intensive (mean A1C ~7% [~53 mmol/mol]) versus standard (mean A1C ~9% [~75 mmol/mol]) glycemic management in people with type 1 diabetes, showed definitively that better glycemic status is associated with 50–76% reductions in rates of development and progression of microvascular complications (retinopathy, neuropathy, and chronic kidney disease). Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (44,45) demonstrated persistence of these microvascular benefits over two decades despite the fact that the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto study (46) and UK Prospective Diabetes Study (UKPDS) (47,48) examined the effects of "intensive glycemic control" among people with short-duration type 2 diabetes, although glycemic lowering in these studies was not intensive by current standards (mean A1C was 7.1% vs. 9.4% in Kumamoto and 7.0% vs. 7.9% in UKPDS). These trials found lower rates of microvascular complications in the intervention arms, with long-term follow-up of the UKPDS cohorts showing enduring effects on most microvascular complications (49). These studies highlight the long-term benefits of early glycemic lowering in type 2 diabetes.

Additionally, the DCCT (43) and UKPDS (50) studies demonstrated a curvilinear relationship between attained A1C level and microvascular complications in type 1 and type 2 diabetes, respectively. Thus, on a population level, the greatest number of complications will be averted by taking individuals with diabetes from very high to moderate A1C levels. These analyses also suggest that further lowering of A1C from 7% to 6% (53 mmol/mol to 42 mmol/mol) is associated with added reduction in the

Table 6.3—Summary of glycemic goals for many nonpregnant adults with diabetes

A1C	<7.0% (<53 mmol/mol)*†
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose‡	<180 mg/dL* (<10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for certain individuals. †CGM may be used to assess glycemic status as noted in Recommendations 6.3b and 6.3c. Goals should be individualized based on duration of diabetes, age and life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, impaired awareness of hypoglycemia, and individual considerations (per **Fig. 6.1**). ‡Postprandial glucose may warrant special attention if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, which is generally the timing for peak levels in people with diabetes.

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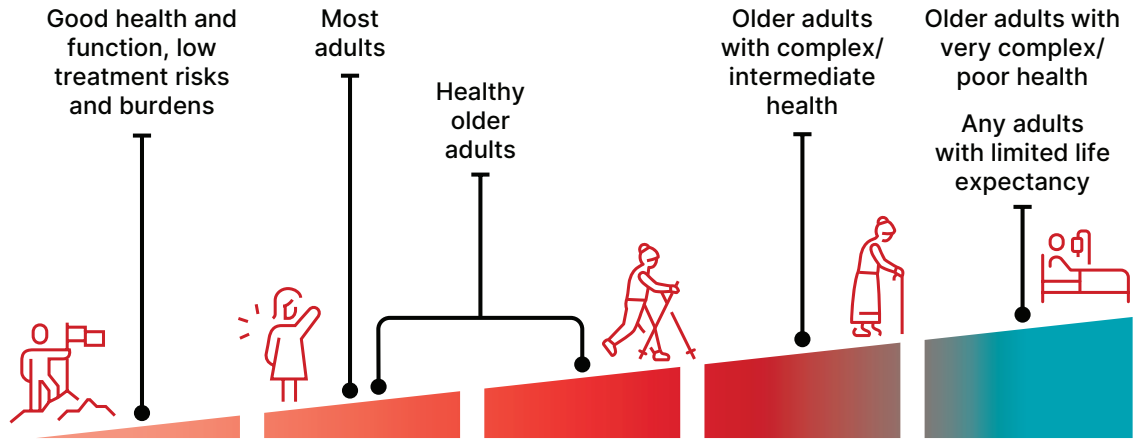
Good health and function, low treatment risks and burdens
Most adults
Healthy older adults
Older adults with complex/ intermediate health
Older adults with very complex/ poor health
Any adults with limited life expectancy

A1C goals	<6.5%	<7.0%	<7.5%	<8.0%	No A1C goal
CGM goals TIR:	—	**>70%**	—	**>50%**	—
• TBR <70	—	<4%	—	<1%	<1%
• TBR <54	—	<1%	—	<1%	<1%
• TAR >180	—	<25%	—	<50%	Avoid symptomatic hyperglycemia
• TAR >250	—	<5%	—	<10%	

Modifying Factors

Favor more stringent goal	Favor less stringent goal
Short diabetes duration	Long diabetes duration
Low hypoglycemia risk	High hypoglycemia risk
Low treatment risks and burdens	High treatment risks and burdens
Pharmacotherapy with cardiovascular, kidney, weight, or other benefits	Pharmacotherapy without nonglycemic benefits
No cardiovascular complications	Established cardiovascular complications
Few or minor comorbidities	Severe, life-limiting comorbidities

Figure 6.1—Individualized A1C and CGM goals for nonpregnant adults. Select the glycemic goal based on individual health and function as described at the top of the figure. Consider modifying to a more or less stringent goal according to the factors listed in the table. Older adults are classified as healthy (few coexisting chronic illnesses, intact cognitive and functional status), as having complex/intermediate health (multiple coexisting chronic illnesses, two or more instrumental impairments to activities of daily living, or mild to moderate cognitive impairment), or as having very complex/poor health (long-term care or end-stage chronic illnesses, moderate to severe cognitive impairment, or two or more impairments to activities of daily living). Select glycemic goals that avoid symptomatic hypoglycemia and hyperglycemia in all individuals. Consider individuals' resources and support systems to safely achieve glycemic goals. Incorporate the preferences and goals of people with diabetes through shared decision-making. CGM, continuous glucose monitoring; TAR, time above range; TBR, time below range; TIR, time in range.

risk of microvascular complications, but the absolute risk reductions become much smaller and may be outweighed by the increasing risk in hypoglycemia when using medications that cause hypoglycemia (e.g., insulin and insulin secretagogues) or requiring glucose-lowering polypharmacy. The implication of these findings is that A1C goals between 6% and 7% are appropriate, and treatment does not necessarily need to be deintensified, in the setting of low hypoglycemia risk, low treatment risks and burdens, and long life expectancy (i.e., sufficient time horizon to derive benefit from glucose lowering). Several glucose-lowering medication classes—notably, metformin, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), dual GIP and GLP-1 RA, dual GIP and GLP-1 RA, sodium–glucose cotransporter 2 (SGLT2) inhibitors, and dipeptidyl peptidase 4 inhibitors—are unlikely to cause hypoglycemia, making it possible for many individuals to achieve lower glycemic goals with a low risk for hypoglycemia (see section 9, "Pharmacologic Approaches to Glycemic Treatment"). Moreover, CGM use was not as common when the DCCT and UKPDS trials were conducted and automated insulin delivery systems were not available; these have been shown to improve glucose levels without increasing hypoglycemia.

Among individuals with type 2 diabetes, three landmark trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease:

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Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) were conducted to examine the effects of near normalization of blood glucose on cardiovascular outcomes. The ADVANCE and VADT trials found modest reduction in nephropathy with intensive glycemic management; ACCORD was stopped after a median of 3.5 years due to higher mortality in the intervention arm (51–55). Importantly, these landmark studies were conducted prior to the approval of GLP-1 RAs, dual GIP and GLP-1 RA, and SGLT2 inhibitors, and intensive glucose lowering was achieved predominantly through greater use of insulin and other medications. Findings from these studies, including the concerning increase in mortality in the intensive treatment arm of ACCORD, suggest caution is needed in treating diabetes to near-normal A1C goals in people with long-standing type 2 diabetes using medications with a high risk for hypoglycemia and with other adverse effects and no additional cardio-kidney-metabolic benefits.

Glucose Lowering and Cardiovascular Disease Outcomes

The DCCT in individuals with type 1 diabetes and the UKPDS, ACCORD, ADVANCE, and VADT studies in type 2 diabetes all sought to address whether intensive glycemic management reduced cardiovascular disease (CVD) events (43,51,52,54). ACCORD, ADVANCE, and VADT were conducted in relatively older participants with a longer duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. Details of these studies are reviewed extensively in the joint ADA position statement "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials" (56). No significant reduction in composite CVD events was demonstrated at the end of the intervention in any of these studies, and ACCORD was stopped prematurely at 3.5 years because of an increase in total mortality, particularly sudden CVD deaths. Serious concerns with the intensive glycemic treatment plan used in ACCORD included the rapid escalation of therapies, the early use of large doses of insulin, substantial weight gain, and frequent hypoglycemia. Blood glucose has subsequently been shown to be a weaker independent CVD risk factor compared with other CVD risk factors, such as hypertension or hypercholesterolemia.

However, a meta-analysis of individual participant data from UKPDS, ACCORD, ADVANCE, and VADT demonstrated a significant reduction in myocardial infarctions and major CVD events but no difference in stroke, heart failure, or mortality between intensive and less intensive glycemic management (57). Additionally, longer-term epidemiological follow-up of these studies also showed a pattern of CVD benefit (58–60). In the post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive treatment arm had a significant 57% reduction in the risk of the composite outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death compared with those previously randomized to the standard treatment arm (58). The benefit of intensive glycemic management in the EDIC cohort of people with type 1 diabetes has been shown to persist for 30 years and was associated with a 32% reduction in CVD events (59).

The UKPDS post-trial 20-year observational follow-up has shown reductions in myocardial infarctions and total mortality both in the group of individuals with overweight treated with metformin and in the group previously treated intensively with sulfonylureas or insulin (49). Post-trial observational follow-up of the VADT over 10 years has also shown a significant reduction in the primary outcome of major CVD events, with myocardial infarctions and heart failure being the most common outcomes (60). In contrast, post-trial observational follow-up of the ADVANCE study in the Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation Post Trial Observational Study (ADVANCE-ON) demonstrated no significant effect on CVD events at 10 years (61). In the epidemiological follow-up of ACCORD in the Action to Control Cardiovascular Risk in Diabetes Follow-On Study (ACCORDION), the excess increase in total mortality that was seen during 3.5 years of intensive treatment was reduced by returning to conventional management, and therefore there was no difference in total mortality after a total of 9 years of follow-up (62). Collectively, results of these studies suggest that long-term intensive glycemic management may reduce CVD events, particularly myocardial infarctions, with heterogeneity of results likely driven by differences in study treatments and populations.

Importantly, these landmark studies in individuals with type 2 diabetes did not include GLP-1 RAs, dual GIP and GLP-1 RA, and SGLT2 inhibitors, which are highly beneficial in subgroups like those included in the trials (i.e., individuals with established CVD and those at high risk for cardiovascular and kidney complications). Subsequent cardiovascular and kidney outcomes trials of these agents were not designed to test higher versus lower A1C; therefore, beyond limited post hoc analysis of these trials, there is limited evidence of the independent cardiovascular and kidney effects of glucose lowering when conferred by these medication classes (63). Indeed, beneficial effects of GLP-1 RA, dual GIP and GLP-1 RA, and SGLT2 inhibitor therapies may be mediated by weight loss, hemodynamic effects, blood pressure lowering, and anti-inflammatory changes rather than glucose lowering per se.

As discussed further below, severe hypoglycemia is strongly associated with cardiovascular events and mortality (64). Therefore, health care professionals should be vigilant in preventing hypoglycemia and should not aggressively attempt to achieve near-normal A1C levels in people in whom such goals cannot be safely and reasonably achieved. As discussed in section 9, "Pharmacologic Approaches to Glycemic Treatment," addition of SGLT2 inhibitors and/or GLP-1–based therapies that have demonstrated CVD and kidney benefits is recommended in individuals with established CVD, chronic kidney disease, and heart failure. As outlined in more detail in section 9, "Pharmacologic Approaches to Glycemic Treatment," and section 10, "Cardiovascular Disease and Risk Management," the cardiovascular benefits of SGLT2 inhibitors or GLP-1 RAs are not contingent upon A1C lowering; therefore, initiation should be considered in people with type 2 diabetes and CVD, kidney disease, heart failure, and/or obesity independent of the current A1C, A1C goal, or metformin therapy. Based on these considerations, the following two strategies are offered (65):

1. If already on dual therapy or multiple glucose-lowering therapies and

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not on an SGLT2 inhibitor or a GLP-1 RA or dual GIP and GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 RAs or a dual GIP and GLP-1 RA in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C goal.

Setting and Modifying Glycemic Goals

Glycemic goals and management should be individualized, with focus on avoiding therapeutic inertia to reduce risks of acute and chronic diabetes complications as well as undue treatment burden and adverse effects of therapy. Multiple factors must be considered when setting a glycemic goal, using shared decision-making to integrate individual needs, goals, and preferences and considering characteristics that influence risks and benefits of therapy. In addition to supporting the establishment of individualized glycemic goals, this approach may optimize engagement and self-efficacy.

The factors to consider in individualizing goals are depicted in **Fig. 6.1**. This figure is not designed to be applied rigidly in the care of a given individual but rather to be used as a framework to guide clinical decision-making (41) and engage people with type 1 and type 2 diabetes in shared decision-making. More aggressive goals may be recommended if they can be achieved safely, with an acceptable burden of therapy (including hypoglycemic risk), and if life expectancy is sufficient to derive benefits of greater glucose lowering. Less stringent goals (e.g., A1C up to 8% [64 mmol/mol]) may be recommended for individuals with complex health status and/or limited life expectancy where benefits of more intensive treatment may not be realized or if the expected risks and burdens of treatment outweigh the potential benefits. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment plans, including setting higher glycemic goals, if the treatment plan requires use of medications associated with high risk for hypoglycemia (i.e., insulin and insulin secretagogues).

Diabetes is a progressive chronic disease; thus, glycemic goals are likely to change over time. Newly diagnosed individuals and/or those without comorbidities that limit life expectancy may benefit from more intensive glycemic goals proven to prevent microvascular complications. Both DCCT/EDIC and UKPDS suggested that there is metabolic memory, or a legacy effect, in which a finite period of intensive glucose lowering yielded benefits that extended for decades after that period ended (44–48). However, there are no data on the long-term effects of early long-term glucose lowering using modern treatment strategies. Thus, a finite period of intensive treatment to near-normal A1C may yield enduring benefits even if treatment is subsequently deintensified as the individual's situation and needs change, clinical complexity increases, and the treatment plan required to lower glucose levels becomes more complex and/or associated with hypoglycemia. Thus, glycemic goals should be reevaluated over time to balance the individualized risks and benefits.

Hypoglycemia is the major risk to individuals treated with insulin, sulfonylureas, or meglitinides, and it is appropriate to deintensify these medications where there is a high risk for hypoglycemia (see HYPOGLYCEMIA RISK ASSESSMENT, below). Switching a high-hypoglycemia-risk medication to lower-hypoglycemia-risk therapy (see section 9, "Pharmacologic Approaches to Glycemic Treatment") should be considered if needed to achieve individualized glycemic goals or where individuals have evidence-based indications for alternative medications (e.g., use of SGLT2 inhibitors in the setting of heart failure or chronic kidney disease and use of GLP-1 RAs in the setting of CVD or obesity). Clinicians should also consider medication burdens other than hypoglycemia, including tolerability, difficulties of administration, impact on education or employment, and financial cost. These factors should be balanced against benefits from glycemic lowering and disease-specific benefits that may be independent of glycemic lowering (section 9, "Pharmacologic Approaches to Glycemic Treatment"). Multiple trials have shown that deintensification of diabetes treatment can be achieved successfully and safely (66–69). It is important to partner with people with diabetes during the deintensification process to understand their goals of diabetes treatment and agree upon appropriate glycemic monitoring, glucose levels, and goals of care (70).

HYPOGLYCEMIA ASSESSMENT, PREVENTION, AND TREATMENT

Recommendations

6.10 Review history of hypoglycemia at every clinical encounter for all individuals at risk for hypoglycemia, and evaluate hypoglycemic events as indicated. **C**

6.11 Screen individuals at risk for hypoglycemia for impaired hypoglycemia awareness at least annually and when clinically appropriate. **E** Refer to a trained health care professional for evidence-based intervention to improve hypoglycemia awareness. **A**

6.12 Screen individuals at high risk for hypoglycemia or with severe and/or frequent hypoglycemia for fear of hypoglycemia at least annually and when clinically appropriate. **E** Refer to a trained health care professional for evidence-based intervention. **A**

6.13 Consider an individual's risk for hypoglycemia (see **Table 6.5**) when selecting diabetes medications and glycemic goals. **B**

6.14 Use of CGM is beneficial and recommended for individuals at high risk for hypoglycemia. **A**

6.15 Glucose is the preferred treatment for the conscious individual with glucose <70 mg/dL (<3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Avoid using foods or beverages high in fat and/or protein for initial treatment of hypoglycemia. Fifteen minutes after initial treatment, repeat the treatment if hypoglycemia persists. **B**

6.16 Glucagon should be prescribed for all individuals taking insulin or at high risk for hypoglycemia. **A** Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it. Glucagon preparations that do not have to be reconstituted are preferred. **B**

6.17 First aid kits should include oral glucose for use in treating hypoglycemia. **C**

6.18 All individuals taking insulin **A** or at risk for hypoglycemia **C** should receive structured education for hypoglycemia prevention and treatment, with ongoing education for those who experience hypoglycemic events.

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6.19 One or more episodes of level 2 or 3 hypoglycemia should prompt reevaluation of the treatment plan, including deintensifying or switching diabetes medications if appropriate. **B**

6.20 Regularly assess cognitive function; if impaired or declining cognition is found, the clinician, person with diabetes, and caregiver should increase vigilance for hypoglycemia. **B**

Hypoglycemia Definitions and Event Rates

Hypoglycemia is often the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations regarding the classification of hypoglycemia are outlined in **Table 6.4** (71). Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for adrenergic responses to falling glucose in people without diabetes. Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, sweating, and hunger (72). Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience impaired hypoglycemia awareness, a measured glucose level <70 mg/dL (<3.9 mmol/L) is considered clinically important, regardless of symptoms. Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [<3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. If an individual has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have impaired hypoglycemia awareness (discussed further in HYPOGLYCEMIA RISK ASSESSMENT, below). This clinical scenario warrants investigation and review of the treatment plan (73,74). Lastly, level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery, irrespective of glucose level.

Hypoglycemia has a broad range of negative health consequences (75). Level 3 hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. Level 3 hypoglycemia was associated with mortality in both the standard and the intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward (76). An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial and in clinical practice (77,78). Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury (79). Hypoglycemia may also cause substantial anxiety that can reduce the quality of life of individuals with diabetes and their caregivers and may contribute to problems with diabetes self-management and treatment (80–82). Recurrent level 2 hypoglycemia and/or level 3 hypoglycemia is an urgent medical issue and requires intervention with treatment plan adjustment, behavioral intervention, delivery of diabetes self-management education and support, and use of technology to assist with hypoglycemia prevention and identification (74,83–86).

Epidemiologic studies of hypoglycemia predominantly rely on claims data to assess hypoglycemia-related hospitalizations and emergency department visits (87–90). These studies do not capture the level 1 and level 2 hypoglycemia that represent the vast majority of hypoglycemic events, and they also substantially underestimate level 3 hypoglycemia (87,91,92). Nevertheless, they reveal a substantial burden of hypoglycemia-related hospital utilization in the community (87–90). Level 1 and level 2 hypoglycemia can be ascertained from individual self-report (93) and are strong risk factors for subsequent level 3 hypoglycemia.

Table 6.4—Classification of hypoglycemia

	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L)
Level 2	Glucose <54 mg/dL (<3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level

Adapted from Agiostratidou et al. (71).

Hypoglycemia Risk Assessment

Assessment of an individual's risk for hypoglycemia includes evaluating clinical risk factors as well as relevant social, cultural, and economic factors (**Table 6.5**). Recommendations 6.10–6.20 group individuals with diabetes into two hypoglycemia risk categories with clinical significance. Individuals at risk for hypoglycemia are those treated with insulin, sulfonylureas, or meglitinides; clinically significant hypoglycemia is rare among individuals taking other diabetes medication classes (94,95). Individuals at high risk for hypoglycemia are the subset of individuals at risk for hypoglycemia who either have a major hypoglycemia risk factor or have multiple other risk factors (determined by the health care professional incorporating clinical judgment) (**Table 6.5**). This risk stratification is based on epidemiologic studies of hypoglycemia risk (88,89,94,96–100). Validated tools have been developed to estimate hypoglycemia risk using predominantly electronic health record data (101–103). However, these tools do not include all of the important hypoglycemia risk factors, and more research is needed to determine how they can best be incorporated into clinical care.

Among individuals at risk for hypoglycemia, prior hypoglycemic events, especially level 2 or 3 events, are the strongest risk factors for hypoglycemia recurrence (95,98,104–106). Hypoglycemia history should be assessed at every clinical encounter and should include hypoglycemic event frequency, severity, precipitants, symptoms (or lack thereof), and approach to treatment. It is essential to correlate glucose readings, both from glucose meters and CGM systems, with symptoms and treatment, as individuals may experience and treat hypoglycemic symptoms without checking their glucose level (107), treat normal glucose values as hypoglycemic, or tolerate hypoglycemia without treatment either because of lack of symptoms or to avoid hyperglycemia. When low sensor glucose readings occur

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Table 6.5—Assessment of hypoglycemia risk among individuals treated with insulin, sulfonylureas, or meglitinides

Clinical and biological risk factors	Social, cultural, and economic risk factors
Major risk factors • Recent (within the past 3–6 months) level 2 or 3 hypoglycemia • Intensive insulin therapy* • Impaired hypoglycemia awareness • Kidney failure • Cognitive impairment or dementia • History of metabolic surgery	Major risk factors • Food insecurity • Low-income status§ • Housing insecurity • Fasting for religious or cultural reasons • Underinsurance
Other risk factors • Multiple recent episodes of level 1 hypoglycemia • Basal insulin therapy* • Age ≥75 years† • Female sex • High glycemic variability‡ • Polypharmacy • Cardiovascular disease • Chronic kidney disease (eGFR <60 mL/min/1.73 m^2 or albuminuria) • Neuropathy • Retinopathy • Major depressive disorder • Severe mental illness • Gastroparesis • β-Blocker therapy	Other risk factors • Low health literacy • Alcohol or substance use disorder

Major risk factors are those that have a consistent, independent association with a high risk for level 2 or 3 hypoglycemia. Other risk factors are those with less consistent evidence or a weaker association. These risk factors are identified through observational analyses and are intended to be used for hypoglycemia risk stratification. Individuals considered at high risk for hypoglycemia are those with ≥1 major risk factor or who have multiple other risk factors (determined by the health care professional incorporating clinical judgment) (88, 89, 94, 96–99, 117, 119, 122, 190, 191, 88, 89, 94, 96–99, 117, 120, 191, 192). Proximal causes of hypoglycemic events (e.g., exercise and sleep) are not included. eGFR, estimated glomerular filtration rate. *Rates of hypoglycemia are highest for individuals treated with intensive insulin therapy (including multiple daily injections of insulin, continuous subcutaneous insulin infusion, or automated insulin delivery systems), followed by basal insulin, followed by sulfonylureas or meglitinides. Combining treatment with insulin and sulfonylureas further increases hypoglycemia risk. †Accounting for treatment plan and diabetes subtype, the oldest individuals (aged ≥75 years) have the highest risk for hypoglycemia in type 2 diabetes; younger individuals with type 1 diabetes are also at very high risk. ‡Tight glycemic management in randomized trials increases hypoglycemia rates. In observational studies, both low and high A1C are associated with hypoglycemia in a J-shaped relationship. §Includes factors associated with low income, such as living in a socioeconomically deprived area.

in low-risk individuals, or occur without associated symptoms, causes of artifactual hypoglycemia should be investigated, such as compression of a CGM sensor during sleep.

Individuals at risk for hypoglycemia should also be screened for impaired hypoglycemia awareness (also called hypoglycemia unawareness or hypoglycemia-associated autonomic failure) at least yearly. Impaired hypoglycemia awareness is defined as not experiencing the typical counterregulatory hormone release at low glucose levels or the associated symptoms, which often occurs in individuals with long-standing diabetes or recurrent hypoglycemia (108). Some individuals with impaired hypoglycemia awareness can sense hypoglycemia, but only at lower glucose levels or with fewer symptoms (109). Individuals with impaired hypoglycemia awareness may experience confusion as the first sign of hypoglycemia, which can create fear of hypoglycemia and severely impact quality of life (109). Impaired hypoglycemia awareness dramatically increases the risk for level 3 hypoglycemia (110). Validated questionnaires for assessing impaired hypoglycemia awareness include the single-question Pedersen-Bjergaard (111) and Gold (112) tools; the Clarke (113) and HypoA-Q (114) tools are longer questionnaires that evaluate multiple domains of impaired hypoglycemia awareness. Comparisons between these tools largely yield good agreement (115,116). To efficiently screen for impaired hypoglycemia awareness in clinical practice, clinicians can ask a single question based on these tools such as "Can you always feel when your blood glucose is low?" and follow "No" responses with a more detailed evaluation.

Other notable clinical and biological risk factors for hypoglycemia are very young age, older age, multimorbidity, cognitive impairment, chronic kidney disease and kidney failure, CVD, depression, neuropathy, and gastroparesis (94,95,117). Female sex has also been found to be an independent risk factor for hypoglycemia in multiple studies, although the mechanisms of this relationship are unclear and require further research (94). Cognitive impairment has a strong bidirectional association with hypoglycemia, and recurrent severe hypoglycemic episodes were associated with a greater decline in psychomotor and mental efficiency after long-term follow-up of the DCCT/EDIC cohort (118). Therefore, cognitive function should be routinely assessed among older adults with diabetes. Hypoglycemia is also a frequent complication for people with diabetes who have undergone metabolic surgery, especially Roux-en-Y gastric bypass (119). Hypoglycemia after metabolic surgery is caused by excessive post-meal endogenous insulin secretion and typically emerges months to years after surgery (120).

There are a number of important social, cultural, and economic hypoglycemia risk factors that should also be considered. Food insecurity is associated with increased risk of hypoglycemia-related emergency department visits and hospitalizations in low-income households, and this was shown to be mitigated by increased federal nutrition program benefits (121). In general, individuals with low annual household incomes (95), individuals who live in socioeconomically deprived areas (98), and individuals who are underinsured (99) or experiencing housing instability (122) experience higher rates of emergency department visits and hospitalizations for hypoglycemia. Clinicians should also be aware of cultural practices that may influence glycemic management (which are discussed in detail in section 5, "Facilitating Positive Health Behaviors and

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Well-being to Improve Health Outcomes"), such as fasting as part of religious observance. Fasting may increase the risk for hypoglycemia among individuals treated with insulin or insulin secretagogues if not properly planned for, so clinicians need to engage these individuals to codevelop a diabetes treatment plan that is safe and respectful of their traditions (123).

Young children with type 1 diabetes and older adults, including those with type 1 and type 2 diabetes (124,125), are noted as being particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glycemic goals, education, nutrition intervention, physical activity management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve outcomes (108). Insulin pumps with automated low-glucose suspend and automated insulin delivery systems have been shown to be effective in reducing hypoglycemia in type 1 diabetes (126). For people with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, pancreas transplant alone or human islet transplantation may be an option, but these approaches remain experimental (127,128). Indeed, recent observational data have shown persistence of severe hypoglycemia even among those that used advanced diabetes technologies and management approaches, highlighting the need for ongoing surveillance of hypoglycemic risk (129,130).

Hypoglycemia Treatment

Health care professionals should counsel individuals with diabetes to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL (3.9 mmol/L) or less (131–133). Individuals should be counseled to recheck their glucose 15 min after ingesting carbohydrates and to repeat carbohydrate ingestion and seek care for ongoing hypoglycemia. Emergency medical services should be called for people who are unalert or unable to administer carbohydrates. These instructions should be reviewed at each clinical visit.

For most individuals, 15 g carbohydrates should be ingested. Individuals using automated insulin delivery systems should typically ingest 5–10 g carbohydrates unless there is hypoglycemia in conjunction with exercise or there has been significant overestimation of a carbohydrate/meal bolus (134). The acute glycemic response to food correlates better with the glucose content than with the total carbohydrate content. Pure glucose is the preferred initial treatment, but any form of carbohydrate that contains glucose will raise blood glucose. People taking acarbose should treat hypoglycemia with only pure glucose, as acarbose inhibits sucrose breakdown, potentially delaying correction of hypoglycemia if sucrose-containing carbohydrates are used (135). Added fat may slow and then prolong the acute glycemic response. Dietary protein intake may increase insulin secretion and should not be used to treat hypoglycemia (136). Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery.

Because hypoglycemia may occur in workplaces, schools, and other institutions and public settings (87,91,92,137), first aid kits (both prepackaged and self-made) should include oral glucose for hypoglycemia treatment. Notably, current guidance for first aid kit composition omits glucose (138,139). Options for oral glucose products include glucose tablets, which have the benefits of a long shelf life and easy dosing, and/or glucose gel products, which generally have a shorter shelf life but may be easier to ingest for children and edentulous individuals. Instructions provided with these products should include guidance to only administer oral glucose to an alert person, to check blood glucose before administering oral glucose and 15 min later, and to administer 15 g of glucose as initial treatment.

Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. All individuals treated with insulin or who are at high risk of hypoglycemia as discussed above should be prescribed glucagon. For these individuals, clinicians should routinely review their access to glucagon, as appropriate glucagon prescribing is very low in current practice (140–142). An individual does not need to be a health care professional to safely administer glucagon. Those in close contact with, or having custodial care of, individuals with diabetes prescribed glucagon (e.g., family members, roommates, school personnel, coaches, childcare professionals, correctional institution staff, or coworkers) should be instructed on the use of glucagon, including where the glucagon product is kept and when and how to administer it. It is essential that they be explicitly educated to never administer insulin to individuals experiencing hypoglycemia. Glucagon was traditionally dispensed as a powder that requires reconstitution prior to injection. However, intranasal and ready-to-inject glucagon preparations are now widely available and are preferred due to their ease of administration resulting in more rapid correction of hypoglycemia (143–145). Although the physical and chemical stability of glucagon has improved with newer formulations, care should be taken to replace glucagon products when they reach their expiration date and to store glucagon based on specific product instructions to ensure safe and effective use. For currently available glucagon products and associated costs, see **Table 6.6**. Health insurance providers may prefer only select glucagon products, so it is important to check individuals' insurance coverage and prescribe formulary products whenever possible.

Hypoglycemia Prevention

A multicomponent hypoglycemia prevention plan (**Table 6.7**) is critical to caring for individuals at risk for hypoglycemia. Hypoglycemia prevention begins by establishing an individual's hypoglycemia history and risk factors, as discussed in HYPOGLYCEMIA RISK ASSESSMENT above. Structured education for hypoglycemia prevention and treatment is critical and has been shown to improve hypoglycemia outcomes (146,147). Education should ideally be provided through a diabetes self-management education and support program or by a trained diabetes care and education specialist, although these services are not available in many areas (148,149). If structured education is not available, clinicians should educate individuals at risk for hypoglycemia on hypoglycemia definitions, situations that may precipitate hypoglycemia (e.g., fasting, delayed meals, physical activity, and illness), blood glucose self-monitoring, avoidance of driving with hypoglycemia, step-by-step instructions on hypoglycemia treatment as discussed above, and glucagon use as appropriate (146).

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CGM can be a valuable tool for detecting and preventing hypoglycemia in many individuals with diabetes, and it is recommended for insulin-treated individuals, especially those using multiple daily insulin injections or continuous subcutaneous insulin infusion. There is clinical trial evidence that CGM reduces rates of hypoglycemia in these populations. CGM can reveal asymptomatic hypoglycemia and help identify patterns and precipitants of hypoglycemic events and provide alarms that can warn individuals of falling glucose so that they can intervene (150,151). CGM may also be helpful to reduce hypoglycemia and improve quality of life in people with hypoglycemia as a complication of metabolic surgery (152,153). For more information on using BGM and CGM for hypoglycemia prevention, see section 7, "Diabetes Technology."

An essential component of hypoglycemia prevention is appropriate modification to diabetes treatment in the setting of intercurrent illness (discussed in detail below) or to prevent recurrent hypoglycemic events. Level 2 or 3 hypoglycemic events in particular should trigger a reevaluation of the individual's diabetes treatment plan, with consideration of deintensification of therapy within individualized glycemic goals.

Individuals with impaired hypoglycemia awareness should be offered training to reestablish awareness of hypoglycemia. Fear of hypoglycemia and impaired hypoglycemia awareness often co-occur, so interventions aimed at treating one often benefit both (154). Several evidence-based training programs have been developed for this purpose and have been demonstrated to reduce rates of hypoglycemia and improve quality of life among people with type 1 diabetes and impaired hypoglycemia awareness (74,155,156). However, these programs are not currently available for clinical use. Similar training can be provided through qualified behavioral health professionals, diabetes care and education specialists, or other professionals with experience in this area, although this approach has not been evaluated in clinical trials. In addition, several weeks of avoidance of hypoglycemia, typically accomplished through a temporary relaxation of glycemic goals, can improve counterregulation and hypoglycemia awareness in many people with diabetes (157). Hence, individuals with impaired hypoglycemia awareness and recurrent hypoglycemic episodes may benefit from short-term relaxation of glycemic goals.

Table 6.6—Median monthly (30-day) AWP and NADAC of glucagon formulations in the U.S.

Product	Form	Median AWP* (min, max)	Median NADAC* (min, max)	Dosage
Glucagon	Injection powder with diluent for reconstitution	$303 ($180, $337)	$242 ($207, $242)	1 mg
Glucagon	Nasal powder	$357	$285	3 mg
Glucagon	Prefilled pen, prefilled syringe	$391	$303 ($303, $304)	0.5 mg, 1 mg
Dasiglucagon	Prefilled pen, prefilled syringe	$371	$298	0.6 mg

AWP, average wholesale price; max, maximum; min, minimum; NADAC, National Average Drug Acquisition Cost. AWP and NADAC prices are as of 1 July 2025. *Calculated per unit (AWP [192] or NADAC [193]); median AWP or NADAC is listed alone when only one product and/or price is described).

INTERCURRENT ILLNESS

Stressful events (e.g., illness, trauma, and surgery) increase the risk for both hyperglycemia and hypoglycemia among individuals with diabetes, particularly in the setting of underlying clinical complexity and polypharmacy. In severe cases, they may precipitate hyperglycemic crises, which are life-threatening and require immediate medical care. Any individuals with diabetes experiencing illness or other stressful events should be assessed for the need for more frequent monitoring of glucose; ketosis-prone individuals also require urine or blood ketone monitoring. Clinicians should reevaluate diabetes treatment during these events and make adjustments as appropriate. Specifically, clinicians should consider holding metformin and SGLT2 inhibitors when oral intake cannot be maintained or if there is concern for acute kidney injury (158). GLP-1 RAs may need to be held for illnesses with significant gastrointestinal

Table 6.7—Components of hypoglycemia prevention for individuals at risk for hypoglycemia at initial, follow-up, and annual visits

Hypoglycemia prevention action	Initial visit	Every follow-up visit	Annual visit
Hypoglycemia history assessment	✓	✓	✓
Hypoglycemia awareness assessment	✓		✓
Cognitive function and other hypoglycemia risk factor assessment	✓		✓
Structured individual education for hypoglycemia prevention and treatment	✓	✓*	✓*
Consideration of diabetes technology needs	✓	✓	✓
Reevaluation of diabetes treatment plan with deintensification, simplification, or agent modification as appropriate	✓	✓†	✓†
Glucagon prescription and training for close contacts for insulin-treated individuals or those at high hypoglycemic risk	✓		✓
Training to improve hypoglycemia awareness	✓‡		✓‡

The listed frequencies are the recommended minimum; actions for hypoglycemia prevention should be taken more often as needed based on clinical judgment. *Indicated with recurrent hypoglycemic events or at initiation of medication with a high risk for hypoglycemia. †Indicated with any level 2 or 3 hypoglycemia, intercurrent illness, or initiating interacting medications. ‡Indicated when impaired hypoglycemia awareness is detected.

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symptoms (158). Thiazolidinediones should be held, and their ultimate reinitiation reassessed on an individualized basis, in the setting of heart failure exacerbation or other conditions with hypervolemia (158). In addition, clinicians should be aware of medication interactions that may precipitate hypoglycemia and modify treatment appropriately. Notably, sulfonylureas interact with a number of commonly used antimicrobials (fluoroquinolones, clarithromycin, sulfamethoxazole-trimethoprim, metronidazole, and fluconazole) that can dramatically increase their effective dose, leading to hypoglycemia (159–161). Clinicians should consider temporarily decreasing or stopping sulfonylureas when these antimicrobials are prescribed. It is important to provide specific, individualized guidance to people with diabetes and their caregivers on steps to prevent, detect, and treat significant hypoglycemia, hyperglycemia, and other adverse events during illness and other stressful events as well as to provide guidance on who to call with questions (including during nonclinical hours) and where to seek help for different levels of clinical acuity with the goal of preventing high-risk illness (158).

For further information on management of hyperglycemia in the hospital, see section 16, "Diabetes Care in the Hospital."

HYPERGLYCEMIC CRISES: DIAGNOSIS, MANAGEMENT, AND PREVENTION

Recommendations

6.21 Review history of hyperglycemic crises (i.e., diabetic ketoacidosis and hyperglycemic hyperosmolar state) at every clinical encounter for all individuals with diabetes at risk for these events. **C**

6.22 Provide structured education on the recognition, prevention, and management of hyperglycemic crisis to all individuals with type 1 diabetes, those with type 2 diabetes who have experienced these events, and people at high risk for these events. **B**

Diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state (HHS) are serious, acute, and life-threatening hyperglycemic emergencies (162). Over the past decade, rates of these hyperglycemic crises have increased in both type 1 and type 2 diabetes (90,163,164). Both DKA and HHS impart a substantial risk of subsequent morbidity and mortality and high associated health care costs (165). This section focuses on hyperglycemic crisis risk factors, prevention, and outpatient management. The diagnostic criteria, clinical presentation, and inpatient management of DKA and HHS are described in section 16, "Diabetes Care in the Hospital."

There are a number of clinical factors associated with an increased risk of hyperglycemic crises (**Table 6.8**). In addition, several studies have reported DKA at the presentation of newly diagnosed type 1 diabetes during or after a coronavirus disease 2019 (COVID-19) infection. The precise mechanisms for new-onset diabetes in people with COVID-19 are not known, but several complex interrelated processes may be involved. Some medication classes can affect carbohydrate metabolism and precipitate the development of DKA and HHS, including glucocorticoids, antipsychotic medications, immune checkpoint inhibitors, and SGLT2 inhibitors. The risk of DKA in people with type 1 diabetes using SGLT2 inhibitors can be 5–17 times higher than that in nonusers. In clinical trials of SGLT2 inhibitors in adults with type 1 diabetes, fasting β-hydroxybutyrate of 0.8 mmol/L or higher increased the risk of DKA in the next month by 3.2-fold (166). Given the recognized risk of DKA with SGLT2 inhibitor use in type 1 diabetes, a number of educational initiatives have been suggested for prevention and early intervention to avert progression to severe DKA (167–170). The anticipated availability of continuous ketone monitoring devices may offer a future approach to preventing DKA with and without SGLT2 inhibitor use in type 1 diabetes (171).

In contrast, observational studies and randomized controlled trials have shown that DKA is uncommon in people with type 2 diabetes treated with SGLT2 inhibitors (0.6–4.9 events per 1,000 patient-years) (172). A meta-analysis of four randomized controlled trials found the relative risk of DKA in participants with type 2 diabetes treated with SGLT2 inhibitors versus placebo or active comparator arm to be 2.46 (95% CI 1.16–5.21), while a meta-analysis of five observational studies found the relative risk to be 1.74 (95% CI 1.07–2.83) (173). Risk factors for DKA in individuals with type 2 diabetes treated with SGLT2 inhibitors include very-low-carbohydrate diets and prolonged fasting, dehydration, excessive alcohol intake, and the presence of autoimmunity, in addition to typical precipitating factors (173,174). Up to 2% of pregnancies with pregestational diabetes (most often type 1 diabetes) are complicated by DKA. The incidence of DKA in gestational diabetes is low (<0.1%) (175). Pregnant individuals may present with euglycemic DKA (glucose <200 mg/dL [11.1 mmol/L]), and the diagnosis of DKA may be hindered by the presence of mixed acid-based disturbances, particularly in the setting of hyperemesis. Due to significant risk of fetomaternal harm, pregnant individuals at risk for DKA should be counseled on the signs and symptoms suggestive of DKA and seek immediate medical attention if concern for DKA is present.

Hyperglycemic crisis should be considered in all individuals presenting with polyuria, polydipsia, weight loss, vomiting, dehydration, and change in cognitive state. Individuals at risk for DKA should be counseled on the early signs and symptoms of DKA, provided with appropriate tools for ketone measurement (urine and/or blood ketone tests), and educated on timely self-management of hyperglycemia and hyperketonemia ("sick day advice") (176–178) to prevent clinical deterioration and need for acute care. Clinicians should review DKA prevention practices and availability of ketone monitoring tools at each visit. Individuals treated with intensive insulin therapy should not stop or hold their basal insulin even if not eating, and clinicians should provide detailed instructions on insulin dose adjustments in the setting of illness or fasting to prevent DKA occurrence and worsening. Individuals concerned about or experiencing DKA should be encouraged to contact their diabetes care team immediately. Readily available clinical support can help individuals self-manage hyperglycemia during illness and prevent emergency department and hospital care (179). Individuals at risk for DKA should measure ketones in the presence of symptoms and potential precipitating factors (e.g., illness, missed insulin doses, eating disorders), particularly if glucose levels exceed 200 mg/dL (11.1 mmol/L). Use of blood ketone monitoring compared with urine ketone monitoring in a single 6-month randomized controlled clinical

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Table 6.8—Risk factors for hyperglycemic crises

Type 1 diabetes/absolute insulin deficiency
Younger age
Prior history of hyperglycemic crises
Prior history of hypoglycemic crises
Presence of other diabetes complications
Presence of other chronic health conditions (particularly in people with type 2 diabetes)
Presence of behavioral health conditions (e.g., depression, bipolar disorder, and eating disorders)
Alcohol and/or substance use
High A1C level
Insulin rationing
SGLT2 (SGLT1/2) inhibitor use
Social determinants of health

SGLT, sodium–glucose cotransporter. Data are from McCoy et al. (194), Gibb et al. (195), Randall et al. (196), Thomas et al. (197), and Borden et al. (198).

trial reduced the risk of hospitalization/emergency room management by approximately 50% (180). When hemodynamically and cognitively intact, able to tolerate oral hydration, and able to administer subcutaneous insulin, individuals may treat mild DKA with frequent blood glucose and urine or blood ketone monitoring, noncaloric hydration, and subcutaneous insulin administration. However, individuals should seek immediate medical attention if they are unable to tolerate oral hydration, they experience ongoing emesis, blood glucose levels and/or ketone levels do not improve with insulin administration, altered mental status is present, or any signs of worsening illness occur. Because HHS is associated with greater volume depletion and is typically triggered by an acute illness, individuals with suspected HHS should be immediately evaluated and treated in the inpatient setting.

A substantial proportion of individuals hospitalized with DKA experience recurrent episodes (181,182), which underscores the importance of engaging individuals experiencing these events to identify triggers and prevent recurrence. Structured diabetes self-management education and support that includes problem-solving is effective at reducing DKA admissions, as are psychological interventions, peer support, individual coaching, and behavioral family systems therapy (183,184). Given that asubstantial proportion of DKA in people with established insulin-treated diabetes arises from challenges with self-management, those with recurrent DKA often require extensive multisystemic behavioral interventions (185). Young people with established diabetes in the pediatric age-group, especially during adolescence, experience greater rates of DKA than adults with diabetes (186). Notably, the majority of DKA cases occur in those with established diabetes compared with those with newly diagnosed diabetes, often in association with psychosocial challenges, such as disordered eating behaviors, and during periods of transition, such as from pediatric to adult health care when there may be gaps in ambulatory care (186–188). In addition to challenges with self-management related to missed or inadequate insulin doses as noted above, a number of factors have been associated with DKA, including female sex, designation as part of an underrepresented group (notably by race and ethnicity or by migration background), higher A1C levels, and higher insulin units/kg/day (likely reflecting an increase in dose in response to a higher A1C that likely resulted from missed insulin) (186–188). Other factors associated with DKA include age 10–14 years, public insurance, and prior episodes of DKA; use of insulin pump therapy does not appear to be associated with increased DKA occurrence in the current era.

Individuals who have experienced DKA or HHS should be screened for social determinants of health that can contribute to or trigger these complications, including inadequate access to insulin, other glucose-lowering medications, and diabetes durable medical equipment (i.e., glucose monitoring and insulin administration devices), and referred to appropriate health care and/or community services to mitigate these barriers to care (see section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for additional details). Access to CGM may also decrease risk of DKA recurrence (189).

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